THE RELATION BETWEEN THE THYROID AND PARATHYROID GLANDS.

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PLATE 42.

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Although the thyroid and parathyroid glands are generally regarded as independent organs, numerous observations seem to indicate a functional cooperation between them. These views are based essentially on the microscopic changes that take place in one of the glands after entire or partial extirpation of the other. Although both glands under normal conditions present different and characteristic structures, they may, especially the thyroid gland, under various experimental conditions, undergo structural changes.

The opinions generally held regarding this question are as follows: (1) After parathyroidectomy hypertrophy of the thyroid gland develops (Edmunds,[1] Vassale and Generali,[2] Halpenny and Thompson[3]). (2) After complete removal of the thyroid gland with the enclosed parathyroidea interna, hypertrophy of the parathyroidea externa occurs, with a tendency to the formation of colloid alveoli; in other words, the structure becomes like that of the thyroid (Halpenny and Thompson,[3] Vincent and Jolly,[4] Blum,[5] and Kishi[6]). For these rea-

[1] Edmunds, W., Further Observations on the Thyroid Gland (VI.) *J. Path. and Bacteriol.*, 1907–08, xii, 101.

[2] Vassale, G., and Generali, F., Fonction parathyréoïdienne et fonction thyréoïdienne (Résumé), *Arch. ital. biol.*, 1900, xxxiii, 154.

[3] Halpenny, J., and Thompson, F. D., On the Relationship between the Thyroid and Parathyroids, *Anat. Anz.*, 1909, xxxiv, 376.

[4] Vincent, S., and Jolly, W. A., Some Observations upon the Functions of the Thyroid and Parathyroid Glands, *J. Physiol.*, 1905, xxxii, 65; Further Observations upon the Functions of the Thyroid and Parathyroid Glands, *ibid.*, 1906, xxxiv, 295.

[5] Blum, F., Die Schilddrüse als entgiftendes Organ, *Virchows Arch. path. Anat.*, 1899, clviii, 495.

[6] Kishi, K., Beiträge zur Physiologie der Schilddrüse, *Virchows Arch. path. Anat.*, 1904, clxxvi, 260.

sons most investigators regard both glands as cooperating physiologically, but not as identical.

Before reporting my experiments, I shall describe the changes that may occur in the thyroid that has not been subjected to surgical procedure. We know from earlier observations that the thyroid gland reacts macroscopically and microscopically to various influences. That it sometimes increases in size during pregnancy has long been known. Bircher[7] has produced hypertrophy experimentally in rats and dogs by giving them water from districts where goiter is prevalent among the inhabitants. Halsted[8] was among the first to call attention to the frequent appearance of hypertrophy of the thyroid gland in dogs, without being able to give a satisfactory explanation in all cases.

In a previous publication[9] I showed that an excessive meat diet will cause constant changes in the thyroid glands of rats. The changes consist chiefly of an increase in the weight of the glands (50 per cent), of a proliferation of the epithelial cells, and of a decrease of the colloid substance. Similar experiments with the same results have been previously performed by Watson[10] and others.

The Thyroid Gland after Meat Diet.

Thyroid glands were taken from five cats which for a period of from 8 to 15 months had lived in the laboratory entirely on a diet of meat and water. The same changes previously observed in rats occurred in the cats; *i.e.*, enlargement of the gland, proliferation of the cells, and disappearance of the colloid substance (Fig. 1).

The enlarged gland was weighed in only one instance. This animal, which weighed 3,100 gm., died during an operation as a result of the

[7] Bircher, E., Zur experimentellen Erzeugung der Struma, zugleich ein Beitrag zu deren Histogenese, *Deutsch. Z. Chir.*, 1910, ciii, 276.

[8] Halsted, W. S., An Experimental Study of the Thyroid Gland of Dogs, with Especial Consideration of Hypertrophy of This Gland, *Johns Hopkins Hosp. Rep.*, 1896, i.

[9] Tanberg, A., Om virkrungen ad ensidig kjödernoring, sorlig par glandula thyroidea, *Norsk Mag. Lægevidensk.*, 1910, viii, 516.

[10] Watson, D. C., The Rôle of an Excessive Meat Diet in the Induction of Gout, *Lancet*, 1905, i, 347.

anesthetic, after living on meat for 15 months. In this case the thyroid gland weighed 0.97 gm., and was thus more than three times as large as normally (0.25 to 0.30 gm.). In the other animals the enlargement can only be roughly estimated, but it became evident by a later operation that the thyroid gland was enlarged to about double the normal size.

The proliferation of the cells was pronounced in all cases, although the details varied microscopically. Instead of the regular alveoli lined with a single layer of cells, irregular and often ramified spaces were found. These are produced by proliferation of the epithelium which retains the character of a single layer only in a few places, and protrudes from the wall in solid broad masses, as bud-like proliferations, like partition walls of irregular and sometimes ramified forms. The more compact formations often give rise to small round cavities that probably represent the formation of new alveoli. In these cases the alveolar structure is thus fairly preserved, but in other cases one finds a proliferation which is so strong that the tissue is quite solid, and only an irregular space indicates the remains of earlier alveolar cavities. In the parts where the tissue is more compact the cells lie closely packed without any characteristic arrangement, but in some places there seems to be a tendency toward the formation of small alveoli. The increase of the interstitial connective tissue is negligible. The colloid substance had disappeared and the alveoli are filled with a transparent or slightly granular substance.

It will appear from this description that the hypertrophy caused by a meat diet corresponds with the hypertrophy that develops in the small pieces of the thyroid gland which are left after incomplete thyroidectomy. This is shown in Fig. 2, from a cat on which 10 months previously a bilateral thyroidectomy was performed with retention of both parathyroid glands. After the operation the animal was doing well, and there were no symptoms of tetany or cachexia. At autopsy small pieces of thyroid tissue the size of a pea were found.

On microscopic examination the epithelial layers are seen to have multiplied in many places and to protrude in the form of partition walls and irregular proliferations. No colloid substance was found in the alveoli.

The similarity of the two microscopic pictures is evident. The pro-

liferation of the cells seems to take place according to the same principle, and in both cases the colloid substance also disappears. It therefore seems justifiable to conclude that an excessive meat diet gives rise to an increased activity of the thyroid gland.

The Parathyroid Gland after Meat Diet.

In the animals which had been fed on meat for a long time, the parathyroid gland was also examined in order to find possible changes in the macro- and microscopic appearance. On the whole, microscopically the parathyroid gland is normal in appearance, especially as regards the arrangement of the cells. Small syncytial cells are rare, but these may also be absent in normal glands. Hence relatively large cell forms are generally observed. It should be emphasized that the cells of the parathyroid gland do not react in the same way as those of the thyroid gland on an excessive meat diet, and we may therefore conclude that there is a difference in the functions of the cells of these organs.

Whether an increase in the size of the parathyroid gland occurs cannot be determined by the experiments performed. In organs of such small dimensions and so irregular in appearance, it is difficult to ascertain whether the size is normal.

It is possible that the size of the parathyroid gland may vary according to the diet and way of living. In this connection it should be recalled that a considerable difference is found in the weight of the parathyroid gland in man and in oxen. Vincent[11] gives the average weight of each of the glands in man as 0.035 gm. I have removed the glands in oxen for opotherapeutic experiments and noted that they were considerably smaller than in man. The average weight was 0.021 gm. It is not improbable that differences in diet and metabolism may account for the relatively small parathyroid in oxen.

I have attempted to show that an excessive meat diet may develop hypertrophy of the thyroid gland. This does not mean that other causes for similar changes in the gland may not exist, and the results of surgical operations must be confirmed microscopically by serial sec-

[11] Vincent, S., Innere Sekretion und Drüsen ohne Ausführungsgang, *Ergebn. Physiol.*, 1911, xi, 218.

tions in all cases. This is especially necessary where the larger part of the organs has been extirpated, and where it is of importance to identify all the small remaining pieces.

I shall not mention here the results of experimental extirpation of the parathyroid and thyroid glands from the clinical point of view. I shall merely state that complete parathyroidectomy always resulted in fatal tetany, and complete thyroidectomy in chronic cachexia. Fatal tetany can be prevented only by leaving part of the parathyroid gland, and part of the thyroid must be left in order to prevent cachexia thyreopriva. I shall report only the experiments which seem to indicate a mutual relation between the glands, as far as this can be determined microscopically. The investigations will therefore deal with the changes that occur in one of the organs after entire or partial extirpation of the other.

The Appearance of the Thyroid Gland after Parathyroidectomy.

When the experimental animals died of acute tetany in the course of the first few days after parathyroidectomy, no noteworthy changes were found in the structure of the thyroid gland. The gland had in all cases the same appearance as at the time of operation. The result is different when a protracted insufficiency occurs after the operation, especially in chronic tetany.[12]

In three of my experimental animals chronic tetany developed after extirpation of three parathyroid glands. The animals died after 8, 10, and 11 months, respectively, and there was thus ample opportunity of observing the results that insufficiency of the parathyroid gland would cause in the macro- and microscopic appearance of the thyroid gland. The same results were obtained in all three cases.

The thyroid gland was not enlarged; it was possibly a little smaller than normally. Microscopic examination shows that the alveoli which are normally filled with colloid substance are considerably smaller, and of a round, regular shape, and the cells are generally small and low. Compact bits of intervesicular tissue without cavities are also seen, which probably arise from the relatively small

[12] Tanberg, A., Ueber die chronische Tetanie nach Extirpation von Glandulae parathyreodideae, *Mitt. Grenzgeb. Med. u. Chir.*, 1914, xxvii, 575.

dimensions of the alveoli, whereby the section is apt to traverse compact parts of the gland.

According to this the alveoli in the thyroid gland in chronic tetany should be smaller than usual. This, in connection with the relatively small dimensions of the cells, seems to point to a lower activity of the gland by chronic insufficiency of the parathyroid gland; or, in other words, in chronic tetany the thyroid gland becomes slightly atrophied.

The following questions naturally arise in this connection: Is it not possible that this atrophy, which in all cases is slight, is caused by the chronic disease which has lasted during several months, and is it not possible that any other disease of long duration might give rise to the same changes? Is this atrophy specific? Is it due solely to the extirpation of the thyroid gland?

Before taking up these points, I shall mention a peculiarity in the microscopic picture. From the experiments described above it is seen that hypertrophy of the thyroid gland occurs after a protracted meat diet, and no hypertrophy exists in animals suffering from chronic tetany (Fig. 3). On the contrary, atrophy is evident, and yet these animals have for a period of 8 to 11 months lived on meat, which under normal conditions would be sufficient to develop the changes characteristic of this diet. Hence it appears that a meat diet does not cause hypertrophy of the thyroid gland when an insufficiency of the parathyroid gland exists at the same time.

We shall return to the first question. Is the specific cause of the phenomenon to be found in the extirpation of the parathyroid gland? The following observations from Cat 31 support the view that extirpation of the parathyroid is able to influence the structure of the thyroid gland.

Four parathyroid glands were removed on Sept. 22, 1910. After the operation a slight transient tetany ensued. The weight had increased during the last 5 months, and when the animal was killed on Oct. 28, 1911, there were no signs of disease. The cat had lived entirely on meat for 13 months.

On microscopic examination a fifth parathyroid was found enclosed in the thyroid. The thyroid was of normal size (weight 0.28 gm.). Microscopically no proliferation of the cells was found. The structure was, on the whole, of a normal appearance with regular alveoli of ordinary size filled with colloid substance.

In this case the extirpation of four parathyroid glands did not cause chronic tetany, because the fifth remaining gland was sufficient to prevent its development. But in spite of a protracted meat diet no hypertrophy of the thyroid gland occurred, and no other cause could be detected than the extirpation of the parathyroid gland which had been performed 13 months previously. It therefore may be concluded that even if extirpation of the parathyroid gland is not followed by clinically evident signs of insufficiency, a meat diet does not under these circumstances develop hypertrophy of the thyroid gland.

Cat 32 furnished even stronger evidence of this fact. This animal which had been fed on meat for a long time, was operated on Sept. 26, 1910. Two parathyroid glands and some small pieces of the thyroid were removed, which showed microscopically the characteristic signs of a meat diet. On Feb. 13, 1911, the entire right thyroid gland was removed. It presented the typical appearance of hypertrophy caused by a meat diet; *i.e.*, disappearance of the colloid substance, and a pronounced proliferation of the cells, which transformed the entire gland into a compact tissue. Hence extirpation of two parathyroids could not influence the appearance of the thyroid gland. The last operation was followed by a protracted tetany, which, however, was finally cured.

On Oct. 4, 1911, the middle third of the left thyroid gland was removed. Microscopic examination showed that the thyroid gland had lost its previous appearance. The hypertrophy caused by a meat diet had diminished, although the animal had still been fed exclusively on meat. Instead of the earlier compact proliferation small regular alveoli now appeared, being perhaps a little smaller than normally and lined with a single layer of small cuboidal cells. Colloid substance had again collected in the alveoli.

In this case microscopic pictures are seen of three different stages. At the beginning of the experiment the hypertrophy characteristic of a meat diet was present, and the extirpation of two parathyroid glands did not cause any change. After the third parathyroid gland had been removed together with one-half of the thyroid gland, symptoms of insufficiency occurred, which were finally cured. When the animal was operated on for the third time, nothing abnormal could be observed, and it became apparent that the hypertrophy had diminished and that the thyroid gland was almost normal in appearance.

The cause for this change must be found in the operation performed on Feb. 13, 1911, at which the right thyroid gland and the third parathyroid enclosed in it were removed. Extirpation of one of the thyroid glands cannot have caused the changes in appearance, as this, on the contrary, should produce hypertrophy of the remaining gland. The cause must undoubtedly be looked for in the last operation which resulted in a lasting insufficiency of the parathyroid gland. Although this had apparently been removed, the thyroid gland had nevertheless changed its structure. The conclusion may therefore be drawn that in a thyroid gland where pronounced hypertrophy is already present because of a meat diet, this disappears and the gland assumes its normal appearance after the extirpation of a sufficiently large number of parathyroid glands (in this case three).

From these examples it will be seen that extirpation of the parathyroid gland influences the microscopic appearance of the thyroid gland, and that it seems to be of comparatively little consequence whether hypertrophy caused by a meat diet is present or not. It seems to indicate that an insufficiency in the parathyroid gland corresponded to a certain picture of the thyroid, and as this picture is probably the result of a certain degree of functional activity, we come to the conclusion that an insufficiency in the parathyroid gland develops functional changes in the thyroid gland.

This insufficiency need not necessarily be pronounced enough to give clinically distinct symptoms. The thyroid gland, which easily reacts to influences leading to changes in its function (diet, pregnancy, and water from districts where goiter is prevalent among the inhabitants), is also highly sensitive to a reduction in the function of the parathyroid gland. The small alveoli with cuboidal cells and the absence of hypertrophy caused by meat diet seem to imply some loss of function, or, in other words, that an insufficiency of the parathyroid gland inhibits the functions of the thyroid gland. The view that the functions of the parathyroid and thyroid glands are specific does not, however, exclude the occurrence of a functional interaction between the two glandular systems. But it would be difficult to determine its nature and scope on the basis of these experiments alone.

Gley,[13] and more recently, Vincent, Jolly, and others have already suggested a functional cooperation which they believe to be of a vicarious nature. In our experiments, on the contrary, the results of chronic tetany, as well as the influence of parathyroidectomy on hypertrophy caused by a meat diet, seem to imply that insufficiency of the parathyroid gland causes a reduction of the functions of the thyroid gland.

The Appearance of the Parathyroid Gland after Thyroidectomy.

The material for examination was taken from three cats on which complete thyroidectomy was performed with maintenance of both external parathyroids. All the animals had cachexia thyreopriva, with apathy, fall of temperature, etc. They lived from several months up to 1 or 2 years after the operation.

On microscopic examination serial sections from two cases showed no trace of remains of the thyroid gland. In the third animal a small piece was found, hardly larger than a parathyroid gland, which probably had been instrumental in keeping the animal alive during the 3 years when it was under observation, but which had not been sufficient to prevent the development of definite symptoms of thyreopriva. The animal never showed any signs of tetany, in spite of the insufficiency of the thyroid gland, the reason evidently being that both external parathyroids were left.

In all three cases both external parathyroids were identified in serial sections. There was no essential change in their appearance. Microscopically no structure was found resembling the thyroid gland. No increase in the scant colloid substance nor any formation of follicles has been found. The appearance was normal in spite of the fact that the animals lived for a long time with a constant insufficiency of the thyroid gland, and the parathyroid, therefore, should have had ample opportunity to modify its structure and function, if it had this power.

On the other hand, the glands, as a rule, seemed to be larger than usual. In all probability a compensatory hypertrophy developed as a

[13] Gley, E., Recherches sur la fonction de la glande thyroïde, *Arch. physiol. norm. et path.*, 1892, iv, 311.

result of the extirpation of the internal glands. The actual measurements of the hypertrophy cannot be given.

No definite type of cells can be mentioned as characteristic of the hypertrophied gland. As a rule, however, the cells and the nuclei are relatively large and more symmetrical, while in the normal glands the cells are, as a rule, of various sizes, from syncytial-like cells with little protoplasm to the large transparent cells. The cells in the hypertrophied glands are always of the larger variety, and forms with transparent contents as well as forms with more granular protoplasm are to be seen. Oxyphil cells are not observed here or in the normal glands.

These experiments seem to indicate that the parathyroid gland does not undergo structural changes after total thyroidectomy.

Hypertrophy of the Parathyroid Gland.

The comparatively small changes occurring in the external glands after removal of both the internal glands and both thyroids have already been described. It would be natural to assume that these changes would be more pronounced if the animal had only one remaining parathyroid gland and had lived under a constant insufficiency, as is the case in chronic tetany.

It is also evident that the microscopic picture of the parathyroid gland as it appears in this disease does not in all cases agree with the one found in simple hypertrophy where the extirpation has not been extensive enough to give rise to a chronic insufficiency.

Cats suffering from chronic tetany show on microscopic examination that the remaining parathyroid gland may sometimes assume an appearance which does not present any point of resemblance to the previous descriptions of hypertrophied glands (Fig. 4).

Even under low magnification the microscopic aspect is pronounced in large transparent cells. Under normal conditions the parathyroid cells (Fig. 6) are comparatively little larger than those of the thyroid gland. This is also the case with the nuclei; often hardly any difference in this respect is observed. In this case, however, the contrast in the dimensions of the cells is striking, and is furthermore emphasized by the fact that the thyroid cells in chronic tetany are, if anything, smaller than usual.

With high magnification the following details can be seen: The cells are large, of round, angular, or irregular shape, and with distinct cellular limits. The nuclei are large, eccentric, and rich in chromatin; as a rule, they are round or oblong, but angular forms are frequently seen. The contents of the cells are somewhat varied, but the most characteristic feature is that the greater part of the contents, which surrounds the nuclei to a greater or less extent and often fills the entire cell, is colorless and transparent. Generally along the walls of the cells a small border of granular or filiform protoplasm is seen which without any distinct limit runs into the central transparent part. Sometimes the granular protoplasm is more distended, but even then a more transparent zone can be seen around the nucleus. Distinct vacuoles are nowhere to be seen. The vascularization is ample, and the perivascular tissue somewhat increased, so that the substance of the gland assumes the appearance of being divided into several otherwise not very distinct lobules. No round cellular infiltration is seen.

As already mentioned, the cells, as well as the nuclei, are considerably larger than those generally observed under normal conditions (Fig. 6). While the normal cells of the parathyroid glands measure from 6 to 12μ in diameter, the cells in this instance ranged from 12 by 15μ to 21 by 24μ, or about double the normal diameter. That the nuclei also considerably exceed the normal size is shown in Fig. 4.

Hypertrophy of the Remaining Parts of the Thyroid Gland.

It is well known that when large parts of the thyroid gland are removed, the remaining parts become hypertrophied. Fig. 2 shows distinctly the more characteristic features of this hypertrophy. This form of hypertrophy generally occurs in cases where the remaining parts of the gland have been so large that they are sufficient to prevent the development of cachexia thyreopriva. However, when the remaining pieces are too small to prevent these symptoms, the proliferation of the cells is more pronounced.

Fig. 5 shows the small remaining parts of thyroid tissue found in animals which have suffered for a long time from cachexia thyreopriva.

The gland is for the most part transformed into compact tissue, con-

sisting of closely packed, sharply defined cells of irregular, round, oval, or angular shapes, with nuclei of various sizes rich in chromatin. The protoplasm is also often heterogeneous, in that the cells with strongly granular protoplasm alternate with cells of more transparent and more homogeneous contents.

The arrangement of the cells is usually quite irregular. In several places it is evident, however, that they have retained a tendency to form alveoli, as one often finds small cavities which are more or less filled with granular or filiform contents or sometimes apparently empty. Surrounding these cavities, a long row of evenly arranged cuboidal cells may be observed. Colloid substance is only exceptionally found in the cavities. The tissue is pierced by an ample network of thin anastomosing strings of connective tissue, which in certain places, in the form of thick bundles, divide the gland into distinct lobules. This picture undoubtedly presents certain points of resemblance to the parathyroid gland. It differs in the more irregular shape and arrangement of the cells, in the richer development of connective tissue, and in the pronounced tendency to form small alveoli. Unless serial sections of the remaining parts of the thyroid are examined they may be mistaken for a parathyroid, which structurally shows a transition picture to the thyroid gland.

CONCLUSIONS.

The following conclusions may be drawn from the experiments presented in this article.

1. Excessive meat diet develops hypertrophy of the thyroid gland. A definite hypertrophy of the parathyroid gland under the same conditions has not been established. A meat diet does not develop hypertrophy of the thyroid gland when insufficiency of the parathyroid gland exists at the same time, even if no clinical symptoms are present. Where a pronounced hypertrophy caused by a meat diet has already developed, the hypertrophy disappears and the gland assumes its ordinary appearance after extirpation of a sufficiently large number of parathyroid glands.

2. After parathyroidectomy no hypertrophy of the thyroid gland takes place. In chronic tetany the thyroid gland seems, on the contrary, to atrophy in spite of a meat diet.

3. After complete extirpation of the thyroid gland, the parathyroid gland does not change its structure, even in cases where the cachexia lasts for several years. Small remaining parts of the thyroid gland may through hypertrophy develop into compact tissue and thereby seemingly present some points of resemblance to the parathyroid gland.

4. When the parathyroid gland hypertrophies, as in some forms of chronic tetany, this hypertrophy is characterized by the development of large, transparent, sharply defined cells, with large nuclei rich in chromatin.

5. The parathyroid and thyroid glands are independent organs, each having specific functions. This, however, does not exclude the occurrence of a direct or indirect interaction in the functions of the two systems.

6. There is reason to believe that an insufficiency of the parathyroid gland checks to some extent the function of the thyroid gland. No proof of the existence of a vicarious cooperation between the two glands has been established.

EXPLANATION OF PLATE 42.

FIG. 1. Hypertrophied thyroid gland in a cat after 15 months on a meat diet. × 150.

FIG. 2. The remaining parts of the hypertrophied thyroid gland in a cat in which cachexia did not develop after partial thyroidectomy. × 150.

FIG. 3. Atrophied thyroid gland in a cat with chronic tetany. The colloid substance present in the alveoli cannot be seen in the photograph. × 150.

FIG. 4. The parathyroid gland in a cat with chronic tetany. × 150.

FIG. 5. The remaining parts of the hypertrophied thyroid gland in a cat with chronic cachexia. × 150.

FIG. 6. Normal parathyroid gland in a cat. × 150.

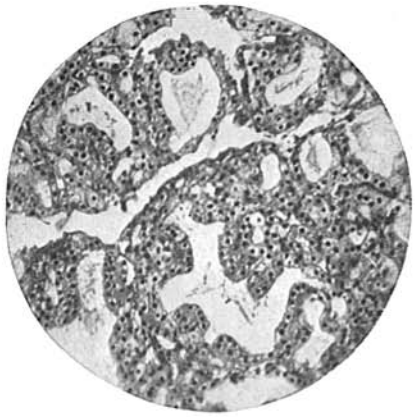

FIG. 1.

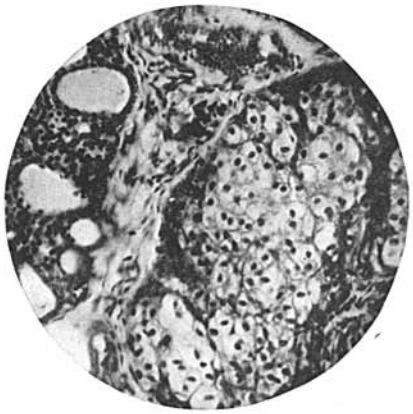

FIG. 4.

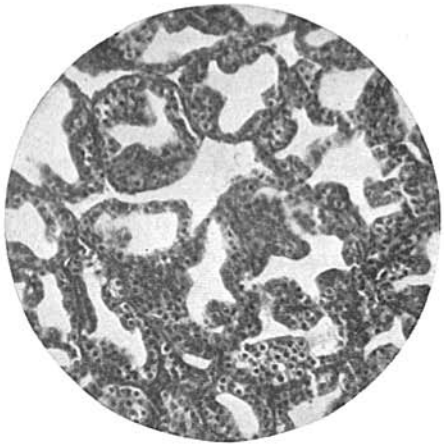

FIG. 2.

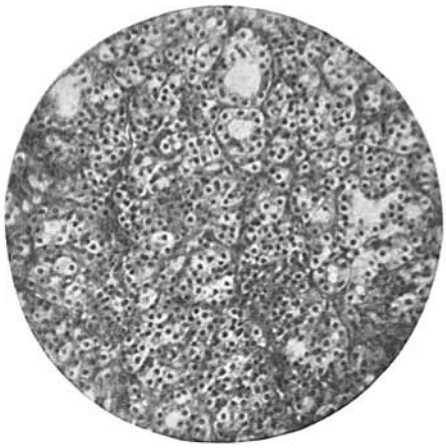

FIG. 5.

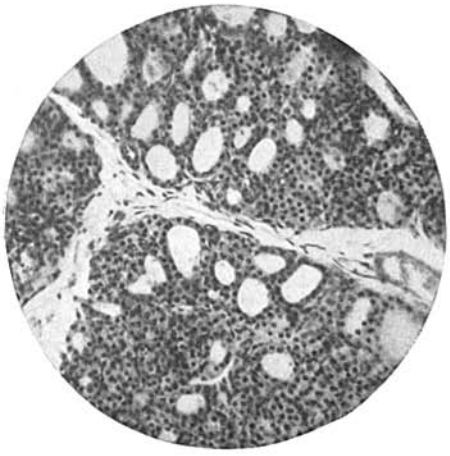

FIG. 3.

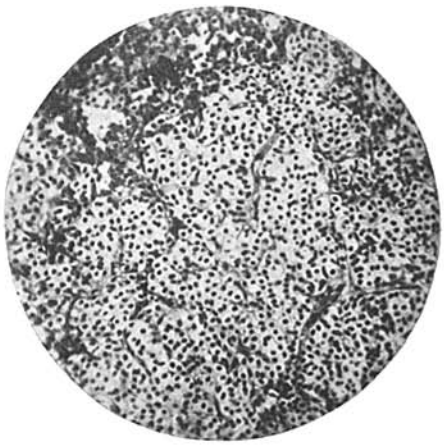

FIG. 6.

(Tanberg: Thyroid and Parathyroid Glands.)